REMARKS

Status of the Claims

Upon entry of this paper, claims 12 and 28-52 are pending, and claims 1-11 and 13-27 are canceled.

Support for Amendments

Claim 12 is amended to incorporate elements from claims 24, 25, and 27. Support for the amendment can be found in the specification as filed, for example on page 12, lines 1-3, and lines 20-24, and Examples 1-3. Claim 12 is also amended to spell out the acronym for Et 743 as required by the Office Action at page 2, lines 7-10. Support can be found in the specification as filed, for example at page 5, last paragraph.

Claim 29 is amended to present a preferred embodiment of the invention. Support can be found in the specification as filed, for example at page 12, line 2. Claims 36-52 are newly presented to remove multiple dependencies from the claims and to present preferred embodiments of the invention. Support can be found in the previous set of claims and the specification as filed, for example at page 12, line 2, pages 14-16 of the specification and Fig. 1.

Claims 28, 30, and 33 are amended to update dependency according to US practice in view of canceled claims 13-17 and 24-27 and amendment of claim 29.

No new matter is added.

No New Issues For Consideration

Claim 12 is amended to incorporate elements from previously examined claims 24, 25, and 27. Claim 29 is amended to present preferred embodiments in separate claims- i.e., in amended claim 29 and in new claim 41. In addition, preferred embodiments from claim 30

are presented separately in claims 36-40 and 48-52. In addition, cancellation of claims 13-17 and 24-27 will simplify the issues for appeal. Therefore, the amendments presented in this paper raise no new issues for consideration, and entry of the amendment is requested.

Information Disclosure Statement

Applicants hereby submit a supplemental Information Disclosure Statement. Applicants request that the references cited therein be considered by the Examiner. In particular, the Villalona-Calero reference in the previous IDS submitted July 16, 2007, was not considered. Therefore, Applicants re-cite the reference and provide a copy of this reference with this paper.

Foreign Priority

The present application is a national phase application of PCT patent application PCT/GB00/01857, filed May 15, 2000 and claims priority to:

(1) GB 9911183.3, filed May 13, 1999,

(2) GB 9911346.6, filed May 14, 1999,

(3) GB 9927005.0, filed November 15, 1999,

(4) GB 9918534.0, filed August 5, 1999,

(5) GB 9927106.6, filed November 16, 1999, and

(6) GB 0007637.2, filed March 29, 2000.

The Examiner has withdrawn the prior acknowledgment of Applicants' claim of priority to these foreign applications and determined that the earliest effective filing date for the claims is May 15, 2000 based on the range of about 500 to about 1650 micrograms/m^2 body surface area. Applicants respectfully traverse in view of the present amendments.

Applicants note that GB 9911183.3, filed May 13, 1999 includes an Example disclosing that 10 patients received a dose of 1500 $\mu g/m^2$ of Et 743 as a 24 hour continuous infusion every three weeks, with two partial responses, two minor responses, and three stabilizations. In addition, GB 9911346.6, filed May 14, 1999 includes an Example disclosing that patients received doses of 1500 $\mu g/m^2$ or over of Et 743 during 24 hour continuous infusions, and partial responses, a minor response, and stabilizations were observed. Therefore, the claims are entitled to the priority dates of GB 9911183.3 and GB 9911346.6.

With regard to GB 9918534.0, filed August 5, 1999, the disclosure indicates infusion times of up to 24 hours, 2-12 hours, 12-24 hours, and 3 hours are disclosed on page 2. Intervals of 2 to 4 weeks are disclosed on page 2. In one example, 11 patients were treated at a dose of 1500 $\mu g/m^2$ or over of Et 743 during 24 hour infusions. Six partial responses, one minor response, and 4 stabilizations were observed. Therefore, the claims are entitled to the priority date of GB 9918534.0.

With regard to 9927106.6, filed November 16, 1999, the disclosure indicates infusion times of up to 24 hours, 2-12 hours, 12-24 hours, 2-6 hours, and 3 hours are disclosed on page 2. Intervals of 2 to 4 weeks are disclosed on page 3. Disclosed dosage includes 1500 $\mu g/m^2$ of Et 743 on the page entitled "Ecteinascidin-743 (ET-743) in heavily pretreated refractory sarcomas: early results of the French experience". Four partial responses, 3 minor responses, and 7 disease stabilizations were reported. Therefore, the claims are entitled to the priority date of GB 9927106.6.

Objection to the Disclosure

The Office Action objects to the disclosure for failing to spell out the acronym for Et 743, and states that Ecteinascidin-743 should be recited at its first occurrence in the independent claim. As required by the Office Action, claim 12 is amended to spell out the acronym for Et 743. In addition, the specification is objected to for failing to provide proper antecedent basis for the term "about" in claims 12 and 15. The objection is moot in view of the amendments presented herein. Applicants request withdrawal of the objection.

Rejection Under 35 U.S.C. 112, 1st paragraph

The Office Action rejects claim 14 for lack of written description. By amendment, claim 14 is canceled. Applicants respectfully request withdrawal of the rejection.

Rejection Under Provisional Obviousness Double-Patenting

Claims 12-17 and 24-35 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-17 of co-pending U.S. Patent Application Serial No. 10/492,320. Applicants traverse on the basis that the claims for US 10/492,320 are directed to administration of Et 743 infused over 3 hours at a dosage below 650 micrograms/m^2/week. In addition, because the rejection is provisional, Applicants respectfully request that the rejection be held in abeyance pending the determination of patentable subject matter. Applicants suggest that if all other rejections are overcome, it is appropriate to withdraw the provisional double-patenting rejection and allow the instant application to issue, as directed by the MPEP:

> If a "provisional" nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed

> of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer. (MPEP §804).

Claims 12-17 and 24-35 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-17 of co-pending U.S. Patent Application Serial No. 10/579,251. Applicants traverse on the basis that the claims for US 10/579,251 are directed to administration of the combination of Et 743 and doxorubicin. In addition, because the rejection is provisional, Applicants respectfully request that the rejection be held in abeyance pending the determination of patentable subject matter. Applicants suggest that if all other rejections are overcome, it is appropriate to withdraw the provisional double-patenting rejection and allow the instant application to issue, as directed by the MPEP:

> If a "provisional" nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer. (MPEP §804).

Rejection Under 35 U.S.C. § 112, second paragraph

Claims 13-17 and 24-35 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite due to the term "about" in the claims. Applicants respectfully traverse. However in order to advance prosecution, the term is removed from the claims. Applicants respectfully request withdrawal of the rejection.

Rejection Under 35 U.S.C. § 103(a)

Claims 12-17 and 24-35 are rejected under 35 U.S.C. § 103(a) for being unpatentable over both Taamma et al. (Eur. J. Cancer, 1997) and Riofrio et al. (23rd European Society for Medical Oncology Congress, abstract, 1998) in view of Goodman&Gilman (1996). Applicants traverse the rejection on the basis that the combination of Taamma, Riofrio, and Goodman&Gilman does not render the instant claims obvious.

U.S. case law holds that a proper obviousness inquiry requires four factual inquiries: (a) determining the scope and contents of the prior art; (b) ascertaining the differences between the prior art and the claims in issue; (c) resolving the level of ordinary skill in the pertinent art; and (d) evaluating evidence of secondary consideration. See *Graham v. John Deere*, 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966). Although the Supreme Court in *KSR* recently rejected a rigid application of the TSM (i.e., teaching, suggestion, motivation) test, the Court did recognize that a showing of "teaching, suggestion, or motivation" to combine the prior art to meet the claimed subject matter could provide a helpful insight in determining whether the claimed subject matter is obvious under 35 U.S.C. § 103(a). See *KSR Int'l Co. v. Teleflex, Inc.*, No 04-1350 at 15 (U.S. Apr. 30, 2007). The Court further noted that an analysis supporting a rejection under 35 U.S.C. § 103(a) should be made explicit, and that "it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *KSR*, slip op. at 14. More recently, the Federal Circuit has explained that a flexible TSM test remains the primary guarantor against a non-statutory hindsight analysis. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007) ("[A]s the Supreme Court suggests, a flexible approach to the TSM test prevents hindsight and focuses on evidence before the time of invention."). The TSM test,

flexibly applied, merely assures that the obviousness test proceeds on the basis of evidence- teachings, suggestions, or motivations- that arise before the time of invention as the statute requires.

Therefore, Applicants respectfully traverse the rejection on the basis that 1) the combination of references fail to teach all of the claimed elements, 2) there is no motivation to combine the references, and 3) the references fail to provide a reasonable expectation of success. These factors provide a helpful insight in determining obviousness, and in view of these factors, the claims are not obvious under 35 U.S.C. § 103(a) from the combination of cited references.

1) Failure of the references to teach all of the claimed elements

Claim 12 includes the elements of a method of treatment of a human patient for cancer comprising administering Et 743 at a dose level of 1500 micrograms/m^2 body surface area in cycles by intravenous infusion at intervals of 3 to 4 weeks with an infusion time of 24 hours wherein said treatment results in a reduction in tumor size. None of the cited references teach that treatment results in a reduction in tumor size. On the contrary, Taamma fails to report any results at all. Taamma merely teaches that 11 patients were entered in a study. Taamma fails to provide any additional information on either dosing levels or results. Similarly, while Riofrio discloses dosing levels, the reference fails to report any actual reduction in tumor size. Rather, Riofrio reports nausea and vomiting (grade 2) and transaminase elevation starting 2-4 days after treatment from 600 micrograms/m^2 DL. Finally, Goodman&Gilman is cited for its discussion of dexamethasone as an effective antiemetic in cancer chemotherapeutic regimens. As such, Goodman&Gilman as cited in the Office Action fails to remedy the deficiencies of Taamma and Riofrio in that it lacks any data with respect to Et 743. Apparently, the claim element of a

treatment that results in a reduction in tumor size is supplied entirely from Applicants' disclosure- the very definition of hindsight reconstruction.

For at least the reason that the references cited by the Examiner fail to teach or suggest all the claim elements, Applicants request that the rejection be withdrawn.

2) Failure of the references to provide motivation

Applicants respectfully submit that combined references, in failing to teach the claimed elements, thereby also fail to provide motivation for the invention as claimed. The Examiner indicates that one "would have been motivated to seek an optimal dosing regimen for ET-743 with respect to dosages, infusion times and intervals of administration through no more than routine experimentation" (Office Action, page 7, 1st full paragraph). Applicants respectfully disagree with the Examiner's characterization of the many variables involved in human clinical trials of potentially toxic compounds to arrive at a pharmacotherapeutic window as "routine experimentation". Even assuming, *arguendo*, that routine experimentation is involved in clinical trials, the courts have commented on "routine testing" as follows:

> Due to the fact that chemistry is still largely an empirical science it is easy to characterize inventions in the chemical field as but the result of "routine testing." It cannot be denied that "routine testing" is an essential part of many inventions in the chemical field. But even "routine" testing, whatever that may be, must be guided and directed by the mental concept of the inventor.

In re Fay et al., 347 F2d 597 CCPA 1965). The courts comments with respect to chemistry are even more applicable to biological systems such as human clinical trials for cancer. The prior art cited by the Examiner teaches nothing about the efficacy of the claimed invention resulting in a reduction in tumor size. Furthermore, if Taamma and/or Riofrio had evidence for a treatment that resulted in a reduction in tumor size, such evidence would have been disclosed along with

the evidence (in Riofrio) of toxicity. In fact, Riofrio only reports nausea and vomiting (grade 2) and transaminase elevation starting 2-4 days after treatment from 600 micrograms/m^2 DL.

For at least the reason that the references cited by the Examiner fail to provide motivation, Applicants request that the rejection be withdrawn.

3) Failure of the references to provide reasonable expectation of success

Claim 12 includes the elements of a method of treatment of a human patient for cancer comprising administering Et 743 at a dose level of 1500 micrograms/m^2 body surface area in cycles by intravenous infusion at intervals of 3 to 4 weeks with an infusion time of 24 hours wherein said treatment results in a reduction in tumor size. Applicants have clearly shown in the specification that a dosage of 1500 micrograms/m^2 of Et-743 over 24 hours every 3 weeks provided an improvement in the clinical status of patients treated at this dose. See Examples 1-3 in the specification. In Example 1, Applicants showed that six previously-untreated people with soft tissue sarcoma exhibited stable disease or minor responses, and four people who had prior chemotherapy exhibited stable disease or minor responses. In Example 2, two people had partial responses, and six people had disease stabilization. Finally, in Example 3, four people had partial responses (two of which became post-surgical complete response), three people had minor responses (one of which became post-surgical complete response), and eleven people had disease stabilizations.

While Applicants have shown a clear benefit in their invention as claimed, the Office Action has improperly found the invention obvious through hindsight reconstruction using Applicants' own data. The Office Action's reasoning is improper because there is no reasonable expectation of success in arriving at a reduction in tumor size through routine optimization.

Fields such as petroleum refining and catalytic production of chemicals are amenable to routine optimization through varying reaction temperatures, for example. Logically, when one has a chemical process that is shown to work, one can vary the parameters and at some point arrive at a maximum output. In treating diseases such as cancer, however, the same cannot be said.

It is well-known in the pharmaceutical field that drug candidates often fail during clinical trials. Drug candidates can fail for any number of reasons, such as lack of efficacy *in vivo* despite activity *in vitro* or, as is common in anti-cancer drugs, an unacceptably narrow window of therapeutic efficacy when compared to toxicity effects. In other words, lots of drug trials for cancer fail to arrive at the particular dosing regimen resulting in reduction of tumor size despite the fact that the drugs have entered clinical trials. Routine experimentation is likely to result in a failed drug candidate. If finding an efficacious drug were merely routine based on phase I trials, then many more cancer drugs would be available. In cancer, the end-point of a reduction in tumor size while maintaining acceptable toxicity levels is not guaranteed, and is in fact, highly unlikely when one considers all of the drugs that fail in clinical trials. Simply put, there is no reasonable expectation that one of ordinary skill in the art will achieve a reduction in tumor size according to the claims based on entry of the drug candidate in Phase I clinical trials. The best that can be said of the cited references is that the end result of tumor size reduction is a desired outcome of their teachings, but it is an outcome without a reasonable expectation of success based on the limited teachings in the references and the unpredictable nature of the field.

If arriving at the present invention including a reduction in tumor size were merely a matter of routine optimization, then clearly regulators in the field (such as the Committee for Proprietary Medicinal Products, part of the EMEA, the European agency

responsible for approving human drugs) would have immediately approved Et 743 based on the cited references alone without any need for data. On the contrary, achieving clinical efficacy is not merely a matter of routine optimization, and as a result, the CPMP in 2003 initially refused to grant market authorization for Et 743 in Europe, citing an unfavorable benefit to risk balance as one basis for the decision (see Pharma Mar Press Release, "PharmaMar Receives EMEA Appeal Decision on Yondelis in Soft Tissue Sarcoma", Pharma Mar Grupo Zeltia, <<http://www.pharmamar.com/en/press/news_release.cfm>>, November 20, 2003, cited in a previous IDS and considered by the Examiner on February 27, 2005). In fact, obtaining marketing approval from the EMEA for marketing in the European Union was only recently achieved on September 17, 2007 based on additional data. See the European Public Assessment Report for Yondelis® (trabectedin, Et 743), from the European Medicines Agency (EMEA), which approved Et 743 for treatment of soft tissue sarcoma. A copy is submitted and cited in the attached Information Disclosure Statement, and the report is available at <<http://www.emea.europa.eu/humandocs/Humans/EPAR/yondelis/yondelis.htm>> . According to the European Public Assessment Report for Yondelis®, the official findings of the EMEA are that Et 743 was more effective when it was given once every three weeks than the alternative dosing schedule, and that in patients receiving it once every three weeks, it took an average of 3.8 months for their disease to get worse, compared with 2.1 months in those receiving Et 743 three times per month. This is a surprising result and in no way is there a reasonable expectation of arriving at this result based on the Office Action's suggestion of mere routine optimization of the Taamma, Riofrio, and Goodman&Gilman references.

For at least the reason that the references cited by the Examiner fail to provide a reasonable expectation of success, Applicants request that the rejection be withdrawn.

In summary, the combination of Taamma and Riofrio and Goodman&Gilman (1) fails to teach or suggest all the claim limitations; (2) fails to teach, motivate, or suggest to those of ordinary skill in the art that they should practice the claimed method; and (3) fails to establish that in practicing the claimed method, there would have been a reasonable expectation of success.

CONCLUSION

Based on the foregoing amendments and remarks, Applicants respectfully request reconsideration and withdrawal of the rejection of claims and allowance of this application.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment to Deposit Account No. **50-3732**, Order No. 13566.105002.

In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. **50-3732**, Order No. 13566.105002.

Respectfully submitted,
King & Spalding, LLP

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By: /michael willis/
Kenneth H. Sonnenfeld / Michael A. Willis
Reg. No. 33,285 / Reg. No. 53,913

Customer Number 65989
Correspondence Address:

King & Spalding
1185 Avenue of the Americas
New York, NY 10036-4003
(212) 556-2100 Telephone
(212) 556-2222 Facsimile